HUNTER: A Conformational Search Program for Acyclic to Polycyclic Molecules with Special Emphasis on Stereochemistry

JÖRG WEISER,* MAX C. HOLTHAUSEN,† LUTZ FITJER

Institut für Organische Chemie der Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany

Received 19 August 1996; accepted January 19, 1997

ABSTRACT: A new conformational search program, HUNTER, connected with the force fields MMP2 and MM3(92) is presented. The program accepts all types of molecules with most different substructures, considers stereochemical facts, and covers conformational space efficiently and completely. The most important facilities are an automated analysis of the stereochemistry including topographical facts, a separate perturbation of the acyclic and cyclic parts of the molecule using modified corner flapping, and an incremental rotation around single bonds with fixed flap and rotation angles, respectively; an exclusion of high energy structures by simulated annealing; the choice of the conformer lowest in energy, which is new as an initial structure for the next sampling run; and the use of a reduced set of dihedral angles to define a conformation. A specifically devised graphic interface, SERVANT, is used to feed in and control all informations necessary for a program run and to visualize the results. Most of the parameters are user-defined and thereby allow a flexible search, including a search for the most stable diastereomer. The efficiency of the different parameter sets was tested in calculation with cycloundecane (**12**), (*Z*)-oct-3-ene (**13**), and sipholenol-A monoacetate (**14**). The best performance regarding the number of different low-energy conformers was achieved with 60° (**14**) and 90°

Correspondence to: L. Fitjer

* Present address: Department of Chemistry, 3000 Broadway MC 3140, Columbia University, New York, NY 10027.

† Present address: Cherry L. Emerson Center for Scientific Computation and Department of Chemistry, Emory University, Atlanta, GA 30322.

Contract/grant sponsor: Fonds der Chemischen Industrie

Contract/grant sponsor: Niederachsen Fund

This article includes Supplementary Material available from the authors upon request or via the Internet at ftp.wiley.com/public/journals/jcc/suppmat/18/1264 or http://journals.wiley.com/jcc/

CCC 0192-8651 / 97 / 101264-18

flaps (**12**), respectively, including substituent correction for the cyclic parts, and with 105° (**14**) and 120° rotations (**13**), respectively, for the acyclic parts. In comparison to the stochastic search routine implemented in MM3(92), HUNTER performed two (**12**) to six (**14**) times better.
J Comput Chem **18:**1264–1281, 1997

Keywords: conformational search; modified corner flapping; stereochemical analysis; MMP2; MM3

Introduction

During the last decade the evaluation of structural properties by means of computational methods has become routine. Today, computational chemistry provides an arsenal of programs for assessing information on geometric, electronic, and dynamic features of chemically interesting systems at a molecular level. Among these, force field programs have become standard tools for conformational analysis. Based on an empirical approach to classical mechanics, and capable of handling the vast majority of molecular classes, these programs show impressive computational efficiency, which enables the user to focus on any relevantly sized molecule. Among the force fields available, MM2[1] is the most widely used, but MM3(92)[2] has set new standards.

Whatever force field is given, the central problem of a conformational search is how to find all relevant low-energy conformations, including the global minimum.[3] Because of a combinatorial explosion, a systematic search of all relevant degrees of freedom is hardly feasible,[4] and therefore most of the programs use a stochastic approach: They generate an initial structure, optimize its geometry, store the resulting conformer if new, and repeat the procedure. Although the fundamental protocol is always the same, distinct differences in the performance of the programs exist. These differences stem from tackling the principal problems of a conformational search:

1. The description of the molecular geometry; that is, the choice between internal (bond lengths, torsion angles, bond angles),[5] geometric coordinates (interatomic distances),[6] or external (Cartesian) coordinates.[7]
2. The alteration of the coordinates; that is, the choice of a perturbation strategy which allows an efficient leaving of the present minimum.
3. The search strategy; that is, the decision of how to combine solutions for 1 and 2 with a search-directing criterion so that the search is efficient and complete.

In what follows, we give some examples: The stochastic search routine[7a] implemented in MM3(92)[2] uses Cartesian coordinates, a random kick incrementation, and an energy-dependent criterion for the selection of the initial structure. This routine has the great advantage of accepting all types of molecules. However, this advantage is in part offset by the fact that large changes in bond lengths and bond angles are introduced, which cause a distinct increase in steric energy. As a result, a considerable amount of computer time is needed for subsequent optimization, which lowers the efficiency of the conformational search. This is especially true for acyclic compounds,[8] whose conformational space is more efficiently covered if internal coordinates are used. Threefold rotations of all torsional angles yield all staggered conformations, whereas all other degrees of freedom (bond lengths, bond angles) are mostly conserved. Therefore, the subsequent optimization is fast and the efficiency of the conformational search is high.[9] Internal coordinates have also been used for cyclic compounds. In this case, one of the bonds is temporarily broken and the remaining torsion angles varied either randomly or systematically, until the ring is closed again. The Monte Carlo multiple minimum search procedure (MCMM),[5c] and the systematic unbounded multiple minimum search procedure (SUMM),[5d] are efficient approaches of this type, albeit most of the intermediate open-chain structures must be rejected because a ring closure would introduce too much strain. This drawback may be avoided if a random variation of the torsional angles within the range of angles compatible with the ring closure is performed.

Other methods for the conformational analysis of cyclic compounds comprise a local variation of the structure through torsional rotation about a ring bond (FLEX),[10a] based on internal coordinates, and a local geometric transformation termed corner flapping[11] (CONFLEX),[12] based on Cartesian coordinates. Both methods are very efficient, and the second[13] will be discussed next. Another recent method termed Low Mode Search (LMOD) has been proven to be equally efficient for acyclic as well as cyclic and bicyclic systems.[10b]

Being engaged in research on the applicability of rearrangements in synthesis,[14] we have long realized that a program allowing an automated educt- and/or product-oriented search for favorable rearrangement paths could open new horizons in terms of creativity and efficiency in the construction of a desired framework. For such a program (CARESY), which has just been completed,[15] we needed a search routine capable of covering the conformational space of a very large number of most different neutral and charged species in a reasonable amount of time. Moreover, as stereochemical aspects play a major role in judging whether a rearrangement is possible or not,[16] an automated analysis of stereoisomers (e.g., enantiomers, diastereomers, *E*-*Z*-isomers) was indispensable. Although force fields have often been used to solve stereochemical problems,[17] none of the search routines available met all our requirements. This is especially due to the fact that most of them are written for acyclic or monocyclic systems only and that, in most cases, the user is not only obliged to determine the stereochemistry and to define stereogenic centers,[18] but must also check each single result for stereochemical consistency. These drawbacks were not considered acceptable. A further drawback was the lack of any possibility defining the stereochemistry of olefins and cumulenes, and distinguishing between diastereomers and enantiomers.[2,5c,7b,12b,18] We therefore decided to develop a new search routine with special emphasis on stereochemistry.

From the very beginning it was clear that the new search routine had to accept all types of molecules (acyclic, monocyclic, bicyclic, polycyclic) with most different substructures (side chains, spirocenters, bridges) and to cover the conformational space efficiently and completely. As a consequence, acyclic parts of a molecule had to be recognized and treated separately by a search routine based on internal coordinates and suitable rotations around each bond. For the cyclic parts of a molecule, the choice of the right strategy was less obvious. However, as all search routines based on internal coordinates and perturbation of the torsion angles of intermediate open-chain structures were thought to produce serious stereochemical and combinatorial problems in going from mono- to polycyclic systems, we decided to base our conformational search on Cartesian coordinates and to use modified corner flapping. The result is a new conformational search program named HUNTER.

General Concept

HUNTER is connected with the force fields MMP2[19] and MM3(92).[2] The calculations presented have been performed with MM3(92). Input structures have been created with PC-Model,[20] and a specifically devised graphic interface, SERVANT, allows feed in and control of all other data necessary for program run. These comprise the definition of the atoms to be flapped, the double bonds to be rotated (rotatable single bonds are recognized automatically), the flap and rotation angles, the chiral centers to be epimerized, and all parameters controlling the simulated annealing[21] used as search-directing criteria. Once an input structure is created, HUNTER analyzes the connectivity and stereochemistry; identifies π-systems, rings, chains, and rotatable bonds; locates bridgehead and spiroatoms; and determines the minimum set of dihedral angles necessary to define the conformation. Then, separate perturbations of the acyclic and cyclic parts of the molecule are performed. During this process, the ring atom to be flapped and the bond to be rotated are chosen randomly. All perturbed structures are subjected to an energy-dependent selection criterion and, after a user-defined number of cycles, the ten lowest in energy are optimized using MM3(92). Of the ten optimized structures thus obtained, the lowest in energy which is new becomes the new initial structure. The programs stops if the user-defined virtual final temperature is reached, if the conformer lowest in energy has been found for a user-defined number of times, if none of the perturbed structures has been accepted, or if the user-defined calculation time has been consumed. Finally, all optimized structure are sorted according to their stereochemistry and energy. A flowchart is given in Figure 1, and the most important methods and procedures are detailed in what follows.

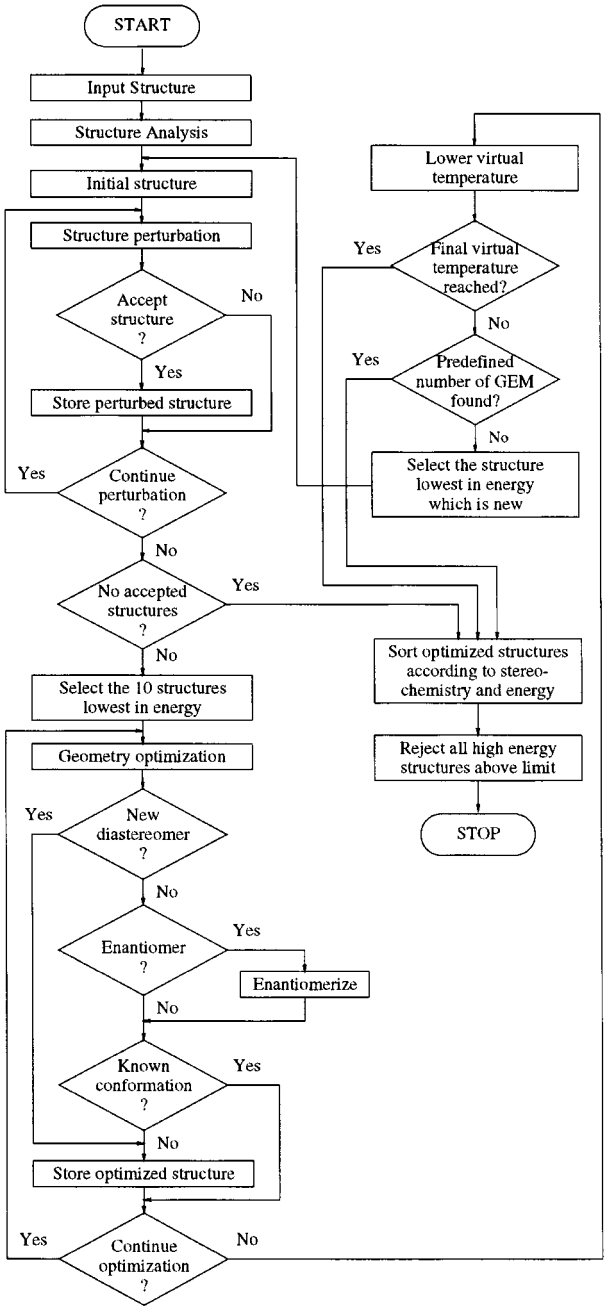


FIGURE 1. Flowchart of the conformational search program HUNTER.

Methods and Procedures

ANALYSIS OF INPUT STRUCTURE

Before any perturbation of an input structure is performed, HUNTER analyzes the connectivity; identifies π-systems, rings, chains, and rotatable bonds; locates bridgehead atoms, spiroatoms, and stereogenic centers; and determines the minimum set of dihedral angles necessary to define a conformation. During a later stage, this last information is used to decide whether a given conformation is new.

CONNECTIVITY OF RINGS

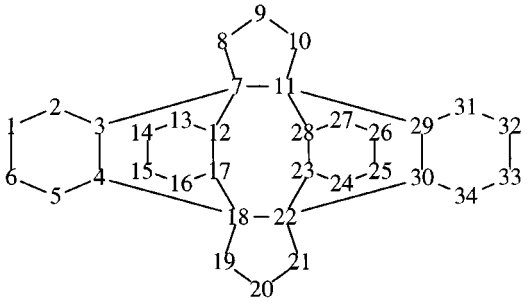
The most common method to describe the connectivity of rings is to search for what is called ''the smallest set of smallest rings (SSSR).''[22] This set is given by the equation of Frèrejacque[23]: $n_{\text{rings}} = n_{\text{ring\_bonds}} - n_{\text{ring\_atoms}} + 1$, and equals the number of rings in planar projection.

To determine the smallest set of smallest rings, HUNTER searches for the shortest way from any ring atom back to the starting point by an optimization procedure. First, the molecule is reduced to the skeleton of ring atoms by making use of the fact that ring atoms differ from nonring atoms by the possibility of returning to the starting point without going a way twice. One of the atoms is then chosen for the search of the smallest ring containing this atom. At every junction, the way to walk is chosen randomly and, therefore, the number of walks, W, must be adjusted to the number of junctions, k. In all cases, it proved sufficient to set $W = 10 \cdot 3^k$.

After a smallest ring has been identified, all ring atoms are stored and are not allowed to be used as starting points for the search of new rings. This guarantees that the smallest set of smallest rings, as defined by HUNTER, never exceeds the Frèrejacque number but sometimes lies below. An example is compound **1** (Fig. 2), where HUNTER defines eight rings, whereas the SSSR algorithm, CRING,[24] defines nine. Indeed, the Frèrejacque number for **1** is nine (42 ring bonds, 34 ring atoms), but the ninth ring (7–11–28–23–22–18–17–12) is clearly dispensable because all of its atoms belong to one of the eight rings already defined.

STEREOCHEMISTRY

For the description of molecules, the determination of their stereochemistry is essential. Because of their complexity, implementation of the Cahn–Ingold–Prelog (CIP) rules[25] in a computer program is difficult,[26] and even in 1982 revised version[25e] deficiencies have been detected.[27] Because of these facts, other stereochemical descriptors have been developed.[28]



1

Ring 1: 1 2 3 4 5 6
Ring 2: 7 3 4 18 17 12
Ring 3: 8 7 11 10 9
Ring 4: 13 12 17 16 15 14
Ring 5: 19 18 22 21 20
Ring 6: 23 28 27 26 25 24
Ring 7: 29 11 28 23 22 30
Ring 8: 31 29 30 34 33 32

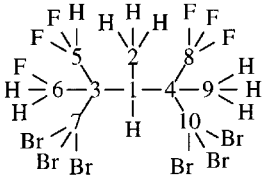
FIGURE 2. The connectivity of rings. The smallest set of smallest rings of **1** as defined by HUNTER.

The stereochemical description in HUNTER is based on the CIP system. However, as a matter of convenience, the order of substituents is derived from the atom types as defined by the force field. HUNTER recognizes *R/S* isomerism in compounds with asymmetric centers, allenes, and cumulenes with an even number of double bonds, and *E/Z*-isomerism in cycloalkanes, olefins, and cumulenes with an uneven number of double bonds. Pseudoasymmetric stereogenic centers (units), whose ligands differ only in topography, but not in topology, are also identified.

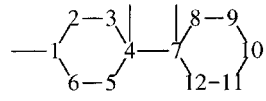
The actual stereochemical analysis consists of three checks which are repeatedly carried out until no more stereogenic centers are found. First, all tetrahedral atoms are checked for chirality by comparing their ligands. After a complete acyclic graph has been developed, this is done by first comparing the atoms directly attached and then, in going from inner to outer spheres, the check sum, *S*, of all triplets of atoms belonging to one and the same sphere according to eq. (1):

$$S = \sum_{T=1}^{T_n} \left[\left(\prod_{i=1}^{m} (A_{Ti} c_{Ti}) \right) \cdot \left(\sum_{i=1}^{m} A_{Ti} \right) \right] \qquad (1)$$

In eq. (1), A means the atom type, c the factor of connectivity (attached atoms: 1; all others: 50), T_n the total number of triplets to be compared, and m the number of atoms within a triplet (maximum: 3). The factor of connectivity, c, has been introduced to prevent hydrogen having a higher priority than carbon. As an example, in the first sphere of compound **2** [atom types: 1 (C), 5 (H), 11 (F), 13 (Br)], hydrogen is recognized as different from carbon. In the second sphere, C-2 [$S = (5 + 5 + 5) \cdot 5 \cdot 5 \cdot 5 = 1875$] is recognized as different from C-3 and C-4 [$S = (1 + 1 + 1) \cdot 50 \cdot 50 \cdot 50 = 375{,}000$], and in the third sphere, C-3 [$S = (11 + 11 + 5) \cdot 11 \cdot 11 \cdot 5 + (11 + 5 + 5) \cdot 11 \cdot 5 \cdot 5 + 13 + 13 + 13) \cdot 13 \cdot 13 \cdot 13 = 107{,}793$] is recognized as different from C-4 [$S = (11 + 11 + 11) \cdot 11 \cdot 11 \cdot 11 + (5 + 5 + 5) \cdot 5 \cdot 5 \cdot 5 + (13 + 13 + 13) \cdot 13 \cdot 13 \cdot 13 = 131\,481$].



2



3

Once this first check has been completed, all tetrahedral ring atoms are checked again and stored as potentially stereogenic, if their substituents are different. If two or more potentially stereogenic ring atoms within a mono- or polycyclic system are found, these are stored as stereogenic. All other potentially stereogenic ring atoms are dismissed. An example is compound **3**, where HUNTER detects three potentially stereogenic centers (C-1,4,7). Of these, two (C-1,4) are stored as stereogenic, whereas the third (C-7) is dismissed. This second check detects cases of *E/Z*-isomerism not recognized by the first check, because no chiral centers are involved. In a third check, the substituents at each end of double bonds and cumulated double bonds are analyzed. If both pairs are different, the corresponding units are stored as stereogenic. *E/Z*- (uneven number of double bonds) and *R/S*-isomerism (even number of double bonds) is thus distinguished.

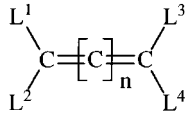
Within a single run, stereogenic centers (units) based on different topographies will be missed. Therefore, based on all previous results, all checks are repeated until no more stereogenic centers (units) are found. At this stage, the priority of ligands, and thereby the stereochemistry, is defined. While going from inner to outer spheres, the following rules are applied:

1. If one ligand differs from all others within one sphere, it becomes the ligand of lowest priority.

2. If two or more ligands differ from each other within one sphere, the check sum S of the triplets of atoms decides; that is, a higher check sum S means a higher priority.
3. If two ligands differ only in their topography, the priority is R over S, and Z over E.
4. For stereogenic ring atoms with two identical ring ligands three cases are distinguished: (a) the ring atom is part of a monocyclic system; (b) the ring atom is a bridgehead atom with an exocyclic ligand (including H); and (c) the ring atom is a bridgehead atom without an exocyclic ligand or a spiroatom. The exocyclic ligands are sorted according to rules 1–3, and the ligand of higher (lower) priority becomes the ligand of highest (lowest) priority. The endocyclic ligands are sorted according to a program internal ring numbering. Albeit arbitrary, this proceeding allows an unequivocal description of relative configuration within rings using the same R/S nomenclature as for absolute configurations.

After the priority of ligands has been determined, the absolute configuration of all stereogenic atoms (units) is defined. For stereogenic atoms the CIP rules are applied, whereas for stereogenic allenes (**4**, $n = 1$) and cumulenes with an even number of double bonds (**4**, $n = 3, 5, 7 \ldots$) the dihedral angle, $\omega_{L^1-C-C-L^3}$, defined by the ligands of higher priority and the end atoms of the double bond system, is determined. For $\omega > 0°$, the configuration is R, otherwise it is S. The absolute value of the same dihedral angle is used for the determination of the configuration of stereogenic olefins (**4**, $n = 0$) and cumulenes with an uneven number of double bonds (**4**, $n = 2, 4, 6 \ldots$). For $0° < |\omega| < 90°$, the configuration is Z, for $90° < |\omega| < 180°$ the configuration is E.

Based on the canonical treatment just described, HUNTER determines the stereochemistry of most organic compounds efficiently and completely. Exceptions are helical structures and compounds which exhibit rotational isomerism around single bonds. In these cases, the concept of determination of stereochemistry through an analysis of connectivities is inadequate.



4

MINIMUM SET OF DIHEDRAL ANGLES

Conformations are most often compared by use of dihedral angles.[29] However, as the comparison of all dihedral angles of a newly generated conformer with a large number of stored conformers may require a considerable amount of computer time, an economic algorithm is important. Therefore, HUNTER uses the minimum set of dihedral angles to define a conformation. Only dihedral angles of the skeleton are considered, whereas dihedral angles to hydrogen atoms are ignored.

In monocyclic systems, the minimum set of overlapping dihedral angles ($\Theta_{1-2-3-4}$, $\Theta_{3-4-5-6}$, etc.) is used to define the conformation. In bicyclic systems, the position of the bridgehead atoms is defined by one further dihedral angle between the rings, and the same is true for the spirocenter of spiranes. Polycyclic systems are treated as combinations of bicyclic systems, and polyspiranes as combinations of monospiranes. Analogously to bridgehead atoms or spirocenters, one further dihedral angle suffices to define the position of a side chain, whereas in the chain itself, all dihedral angles must be defined. In the following, we give some examples (Fig. 3).

The conformation of cyclopentane (**5**), cyclohexane (**6**), and cycloheptane (**7**) is unambiguously described by two (**5**, **6**) and three dihedral angles (**7**), respectively. For the description of spiro[5.4]decane (**8**) and bicyclo[4.2.2]decane (**9**) five and six dihedral angles, respectively, are sufficient. In the first case, two plus two for the rings, and one for the spirocenter, and in the second case, three plus two for the rings, and one for the bridgehead atoms. Three rings in three different bicyclic substructure are contained in tricyclo[7.5.2.$0^{4,15}$]-pentadecane (**10**) and, hence, a total of 11 dihedral angles are needed: two plus three plus three for the rings, and three for the bridgeheads. Finally, five dihedral angles define the conformation of 1-butyl-cyclohexane (**11**): two for the ring, one for the position of the side chain, and two for the chain itself.

We are aware of the fact that, in most cases, the smallest set of dihedral angles necessary to define a conformation will be slightly exceeded. However, the algorithm of HUNTER is easy to implement, valid for all organic compounds, and reduces the total number of dihedral angles consid-

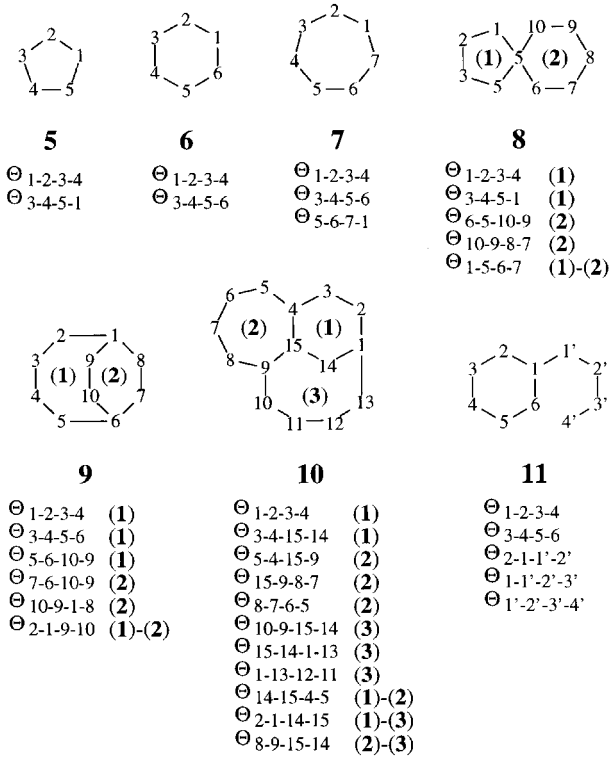


FIGURE 3. The minimum set of dihedral angles of mono- to polycyclic systems as defined by HUNTER.

erably (11 instead of 31 [without H atoms] and 153 [including H atoms], respectively, in the case of **10**).

GEOMETRY PERTURBATION

To guarantee a maximum of efficiency during the later optimization, HUNTER performs the perturbation of acyclic and cyclic substructures separately. We commence with cyclic substructures and first describe the original corner flapping of Goto and Osawa,[11] which we have modified and implemented in HUNTER.

In the original corner flapping (Fig. 4), the corner, *C*, is rotated around the axis *BD* twice an angle $\alpha = 180 - \varphi$, where φ is the dihedral angle between the planes *BCD* and *BDM*, and *M* is the midpoint of the line segment *AE*. Substituents at *B*, *C*, and *D* are carried along. In this way, the main part of the molecule remains unchanged, which guarantees a fast minimization, whereas in most cases barriers to other minima are efficiently crossed. However, conformations exist, especially in large rings, where the original corner flapping does not work because α is zero.[12b,17g] To achieve successful perturbations in these cases also, Goto and Osawa implemented a second algorithm termed edge-flip,[12b] which is a simultaneous flapping of two neighboring ring atoms in opposite directions.

Our solution is different. HUNTER retains the original corner flapping, but with a user-defined fixed flap angle, β, which guarantees a successful perturbation even in cases where α is zero (Fig. 4). Substituents at *B*, *C*, and *D* are carried along, except when they are part of a 1,*n*-bridge with $n \geq 2$. If the flap atom is part of more than one ring, it is randomly chosen which ring will be flapped. Substituents at *C* and substituents at *B* and *D* are treated differently. The former are simply flapped, whereas the latter are readjusted. As exemplified with two substituents S1 and S2 at *B*, we use their orientation with respect to the midpoint *P* of the line segment *AC* to readjust them with respect to the midpoint *Q* of the new line segment *AC″* once the flapping is performed (Fig. 5). In this way, their geometry (bond lengths, bond angles) remains conserved.

In principle, each ring atom not recognized as part of a linear entity (acetylenes, cumulenes) may be flapped. However, two cases should be distinguished: first, the flap-atom is part of only one ring or a spirocenter (Fig. 6); and, second, the flap-atom is a bridgehead atom or part of an endocyclic double bond (Fig. 7). In the first case, low-energy structures are generated and no stereochemical problems are encountered: acyclic sub-

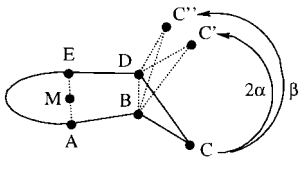


FIGURE 4. Original and modified corner flapping.

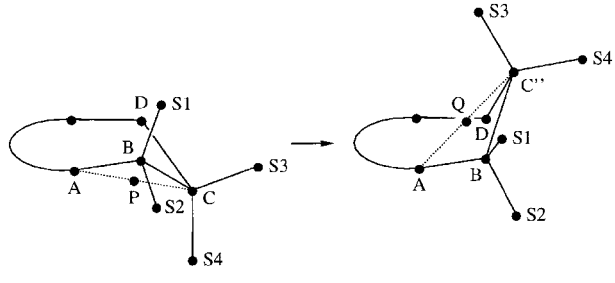


FIGURE 5. The readjustment of substituents.

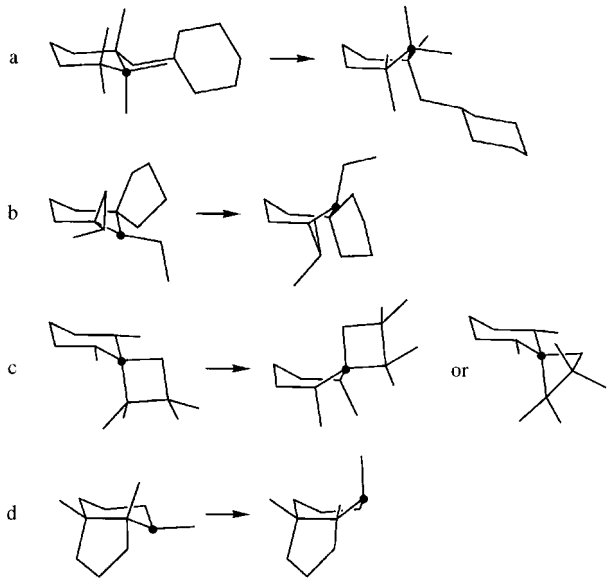


FIGURE 6. The flat atom (•) is part of only one ring or is a spirocenter.

stituents (Fig. 6a–d) and spiroannelated rings (Fig. 6b, c) of any complexity are property readjusted, and even neighboring bridgehead atoms (Fig. 6d) preserve their stereochemistry. In the second case, high-energy structures are obtained and stereoisomerization may occur (Fig. 7a, b).

However, this is by no means restricting, because only these structures are minimized, which pass an energy-dependent selection criterion and belong to the ten structures lowest in energy (Fig. 1). Nevertheless, bridgehead atoms and/or atoms which are part of an endocyclic double bond should not be flapped. As each perturbed structure is the starting structure for the next perturbation, a large number of physically unrealistic structures would result. On the other hand, atoms which are part of only one ring, or which are spirocenters, should always be flapped. In these cases, physically realistic structures of most different geometries will be obtained, whereas the energy increase remains moderate.

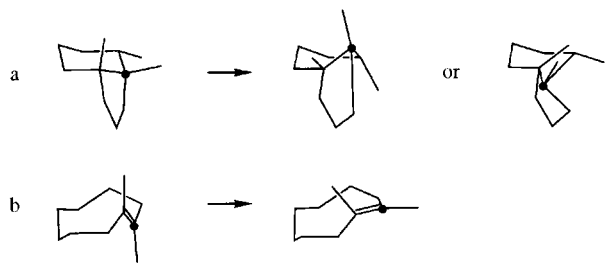


FIGURE 7. The flap atom (•) is a bridgehead atom or part of an endocyclic double bond.

Once the flapping is concluded, the perturbation continues with the rotation around bonds. Rotatable single bonds are recognized automatically and the rotations themselves performed randomly by either the default value (120°) or a user-defined value. Analogous to the flapping process, the number of rotations per perturbation is user-defined or randomly selected between one and the number of rotatable bonds. As result of the automated input structure analysis, the following bond types will be excluded from any rotation: endocyclic bonds, double bonds, triple bonds, C—X bonds, and bonds to CX_3 groups where X are attached atoms. Of these, double bonds may be defined as rotatable.

SEARCHING STRATEGY

Based on the Metropolis Monte Carlo algorithm,[30] simulated annealing[21] has proven to be of outstanding efficiency in finding the global minimum.[31] We use it in connection with other criteria to decide whether a perturbed structure is acceptable or not. This decision has to be made repeatedly during the sampling phase, where an initial structure is perturbed and, if accepted, becomes the initial structure for the next perturbation. Our selection criteria include the following: (1) If the new structure is lower in energy, it is accepted. (2) If the absolute value of the steric energy of the new structure exceeds a user-defined energy window (default value: 50 kcal/atom), it is dismissed. (3) New structures with energies in between are accepted if $\exp(-\Delta E/k_B \cdot T)$ is larger than a random number selected in the interval $[0, 1]$. Thus, movements uphill in energy are allowed, but under the regime of the Boltzmann criterion, it is more and more probable that the only perturbations that survive are those whose energy increase is moderate.

After a predefined number of perturbations, the ten structures lowest in energy are optimized first using the block-diagonal and then the full-matrix Newton–Raphson method to distinguish between minima and transition states. A stereochemical analysis using an R, S-check reveals whether stereo-isomerization has occurred. Enantiomers of the original input structure are mirrored and stored if new, and the same is true for enantiomers of diastereomers that have been found before. New diastereomers are stored as they are.

At this stage of the program run, a user-defined variable controls whether the stereochemistry of the input structure shall be conserved or not. In the former case, only those structures that exhibit the same stereochemistry as the input structure may be chosen as new initial structures. In the latter case, this check is skipped. In both cases, *the structure lowest in energy which is new* is selected as the initial structure for the perturbations of the next sampling phase. The reason is that, in this way, preferentially unexplored regions of the conformational space are covered.[12b] If all optimized structures are known, the last initial structure is used again.

Before a new sampling phase begins, the virtual temperature of the simulated annealing is lowered by a user-defined cooling factor. This means that, in the beginning of a conformational search, energy increasing steps are accepted with a higher probability than in the later phases. The program ends if the virtual temperature has reached a user-defined final value, if the structure lowest in energy has been found for a user-defined number of times, if none of the perturbed structures has been accepted, or if the user-defined calculation time has been consumed. Finally, all structures are sorted according to their energy and stereochemistry.

EPIMERIZATION

HUNTER provides the option of a user-defined epimerization of stereogenic centers, and thereby allows a convenient search for the most stable diastereomer within a single program run. Depending on the stereogenic center (unit) actually involved, different methods of epimerization will be applied:

1. The stereogenic center is part of an acyclic or monocyclic system, or is a spirocenter. This case is modeled by a tetrahedron *ABCD* with M_1 and M_2 as midpoints of the lines *AB* and *CD*, respectively (Fig. 8). To achieve epimerization, HUNTER rotates the substituents *A* and *B* (including the bridge in the case of spiranes) by 180° around an axis *X*, which lies in the plane ABM_2 and passes M_1 perpendicular to *AB*.
2. The stereogenic center is a substituted (a) or unsubstituted bridgehead atom (b). In case (a), the bridgehead atom is defined as the origin of a Cartesian coordinate system and the bond to the substituent as *x*-axis. Then, the substituent is rotated by 180° around the *z*-axis. In case (b), the bridgehead atom is flapped.
3. The stereogenic unit is an exocyclic (a) or endocyclic double-bond system (b). In case (a), the substituents at one end of the double bond are rotated by 180° around the double bond. In case (b), the atoms of the double bond are flapped (flap angle ≥ 90°).

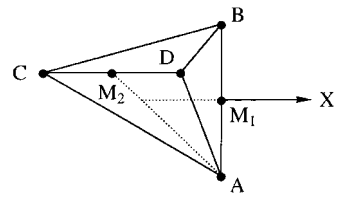


FIGURE 8. The epimerization of a tetrahedral stereogenic center.

In HUNTER, the epimerization is part of the geometry perturbation. This means that epimerizations involving corner flapping are only complete after the subsequent optimizations have been performed.

COMPARISON OF CONFORMERS

As already mentioned, the minimum set of dihedral angles necessary to define a conformation is determined during the analysis of the input structure. Once a minimization is complete, the minimum set of dihedral angles is used to decide whether the resulting conformer is new. Toward this end, the conformer in question is compared with all stored conformers and, if at least one pair of dihedral angles differs by more than 2°, the conformer is recognized as new. In the same way, a conformer with dihedral angles identical in value but opposite in sign to those of an existing one is recognized as an enantiomer and dismissed. To avoid recalculations, the dihedral angles of all conformers are stored separately. Additional time is saved because only dihedral angles of identical stereoisomers are compared.

It is only with unsubstituted cycloalkanes that the atom numbering of a newly generated conformer is permutated and the minimum set of dihedral angles of all permutamers compared with

all previously found conformers. In this way, conformers with different numbering but identical sets of dihedral angles are recognized and not stored as different.

Calculations

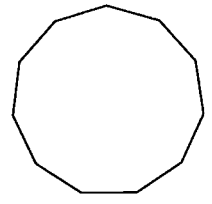
To study the influence of different parameter sets, and to assess the efficiency of HUNTER as compared with the stochastic search routine[7a] implemented in MM3(92),[2] we used three test cases: cycloundecane (**12**) as a cyclic system; (*Z*)-oct-3-ene (**13**) as an acyclic system; and sipholenol-A monoacetate (**14**)[32] as a mixture of both. Because of its conformational flexibility, cycloundecane (**12**) has often been used to assess the ability of a new search routine to cover the conformational space efficiently and completely[33] and, for the same reason, (*Z*)-oct-3-ene (**13**) was used as an acyclic case. However, as both **12** and **13** are unsuitable to mimic structural diversity, a search routine, in a more complicated system, may well prove to be more (or less) efficient than would have been expected from calculations with **12** and **13** alone. Therefore, we decided to restrict the calculations with **12** and **13** to a variation of the flap and rotation angle, respectively, and to use the stereochemically more demanding triterpene sipholenol-A monoacetate (**14**) for in-depth study.

Sipholenol-A monoacetate (**14**) ($C_{32}H_{54}O_5$) consists of a *cis*-configurated bicyclo[5.3.0]decene connected via a rotatable dimethylene bridge to a *trans*-configurated 1-oxa-bicyclo[5.4.0]undecane containing a rotatable acyloxy group as side chain. With a total of 91 atoms, nine chiral centers, and one double bond in structurally most different environments, **14** is clearly a highly demanding test case for the efficiency of a conformational search. An X-ray structure of **14** is known.[32a]

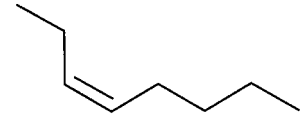
CYCLOUNDECANE AND (Z)-OCT-3-ENE

As recently reported,[29b] the energy surface of cycloundecane (**12**) exhibits 27 MM3-detectable minima, whereas (*Z*)-oct-3-ene (**13**) has not been studied before. We used both compounds for a preliminary check of the efficiency of HUNTER with respect to different flap (Osawa angle, 60°, 90°) and rotation angles (105°, 120°), respectively, and for a comparison with the stochastic search routine implemented in MM3(92). For all calculations, the input structure, a transition state with a steric energy of 68.38 kcal/mol (**12**) and 13.56 kcal/mol (**13**), respectively, was identical. In all calculations with HUNTER, the parameters were as follows: sampling steps: 10; initial virtual temperature: 3000 K; final virtual temperature: 1 K; cooling factor: 0.95 (**13**: 0.96); energy window: 50 kcal/atom; maximum number for finding the global minimum: 500. In the stochastic search with MM3(92) the kick-size was 2.0 Å, as recommended.[2b] All optimizations were performed with the block-diagonal and subsequently the full-matrix optimizer of MM3(92) with a cut-off time of 1.0 min for **12** and 0.2 min for **13**.[34] All calculations were performed with DOS versions of HUNTER and MM3(92), and in all cases identical CPU times (3:00 h on a Pentium 90 processor for **12**; 1:30 h on a Pentium pro 200 processor for **13**) were provided. The results are summarized in Tables I and II.

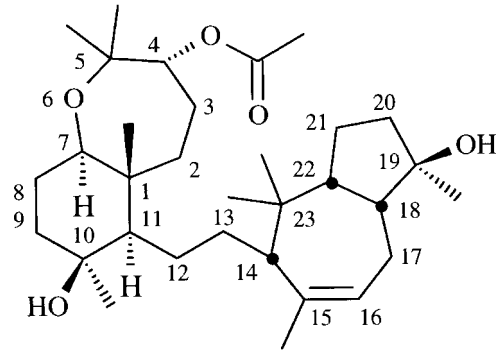
In the case of cycloundecane (**12**) (Table I), all runs with HUNTER were nearly twice as efficient as the run using the stochastic search routine implemented in MM3(92). Of the flap angles used, the 90° angle performed best. In this case all min-



12



13



14

TABLE I.

Calculations on Cycloundecane (12). Results of the Conformational Search Using the Stochastic Search Routine Implemented in MM3(92) and the Search Routine HUNTER with Different Flap Angles.

Conformation	Steric energy (kcal / mol)	MM3(92) kick size 2.0-Å hits	HUNTER, (number of flaps, flap angle) 1, Osawa-flapping hits	1, 60° hits	1, 90° hits
1	28.38	86	134	81	133
2	28.64	33	53	91	58
3	29.56	41	83	32	71
4	29.89	35	37	34	70
5	30.03	8	20	17	14
6	30.30	8	2	86	21
7	31.21	36	65	33	74
8	31.23	34	62	35	61
9	31.27	33	34	16	85
10	31.38	31	88	85	69
11	33.43	21	59	40	34
12	33.69	11	18	27	29
13	34.22	2	3	—	4
14	35.71	4	4	17	11
15	36.40	14	29	48	12
16	36.96	7	23	26	9
17	37.27	4	16	18	22
18	37.82	8	39	43	32
19	38.04	4	—	1	2
20	38.73	5	1	3	4
21	40.75	1	—	2	2
22	41.08	5	35	54	12
23	46.83	—	—	23	2
24	47.51	—	17	7	1
25	48.06	1	3	26	7
26	55.11	—	—	1	10
27	64.66	—	—	—	2
Total hits		432	825	846	851

ima were found, whereas with both other angles and with MM3(92) several minima were missed. In the case of (*Z*)-oct-3-ene (**13**) (Table II), the results from MM3(92) suffered from the fact that a stochastic kick prevents any stereochemical control. As a consequence, most of the perturbed structures were minimized to (*E*)-oct-3-ene. Once again, HUNTER proved to be far more efficient and, of the rotation angles used, the 120° angle performed best. However, as may be seen from the number of hits, the difference in the performance of the three flap and two rotation angles used was not large enough to allow a final judgment. We therefore turned to a stereochemically more demanding case and performed all other calculations on sipholenol-A monacetate (**14**).

SIPHOLENOL-A MONOACETATE

Calculations with HUNTER

As in the case of **12** and **13**, all calculations on sipholenol-A monoacetate (**14**) were performed with the same input structure (steric energy: 143.2 kcal/mol). This structure was obtained through minimization of a stereochemically correct, but arbitrarily chosen, structure of **14** with MM3(92). The following parameters were used: initial virtual temperature: 3000 K; final virtual temperature: 10 K; cooling factor: 0.95; energy window: 4550 kcal (50 kcal/atom); maximum number for finding the global minimum: 25. With one exception, only 15 of the 21 ring atoms of **14** were defined as flap

TABLE II.
Calculations on (Z)-Oct-3-ene (13). Results of the Conformational Search Using the Stochastic Search Routine Implemented in MM3(92) and the Search Routine HUNTER with Different Rotation Angles.

Conformation	Steric energy (kcal / mol)	MM3(92) kick size 2.0-Å hits	HUNTER, number of rotations, angle 1, 105° hits	1, 120° hits
1	7.65	22	78	54
2	7.71	33	64	72
3	7.71	23	45	32
4	7.74	32	71	161
5	8.02	24	56	106
6	8.10	28	56	70
7	8.43	24	47	39
8	8.45	30	42	73
9	8.48	15	64	39
10	8.53	15	92	88
11	8.58	17	67	84
12	8.66	25	46	44
13	8.78	31	59	83
14	8.87	15	59	58
15	9.44	21	45	42
16	9.52	25	59	33
17	9.97	23	53	37
18	10.03	26	55	30
19	11.14	—	22	31
20	11.36	1	17	39
21	11.41	1	18	33
22	11.56	—	11	32
22	11.70	1	—	—
23	11.84	—	14	21
24	11.97	—	10	26
25	12.30	4	8	34
26	12.32	—	11	76
27	12.34	2	11	29
28	13.09	—	19	32
29	13.55	—	8	25
Total hits		438[a]	1207	1523

[a] No stereochemical control. Most of the perturbed structures were minimized to (*E*)-oct-3-ene (43 minima, 1061 hits).

atoms. Bridgehead atoms (C-1,7,18,22) and sp^2 hybridized atoms (C-15,16) were excluded. Moreover, only structures with the same stereochemistry as the input structure were allowed to become the initial structure of a sampling run. All optimizations were performed as described for **12** and **13**, whereas for each run of the local optimizers 5 min of CPU time were provided.[34] All calculations were performed on a DEC Alpha 3000/800 under Unix.[35]

To study the influence of the control parameters to the efficiency of the conformational search, 13 program runs with different parameter sets were carried out. We first tested different combinations of flap and rotation angles (runs 1–6), and then looked for the influence of the number of flaps and rotation (run **7**), the number of flap atoms (run 8), and the number of sampling steps (runs 9, 10), and finally studied the effect of the correction of substituents (run 11), the choice of the initial structure (run 12), and the simulated annealing (run 13). To make the results comparable, each simulation was allowed to run for exactly the same CPU time (16.00 h) on the same computer. This time was chosen such that each run came near to its end, but never reached it. Keeping in mind, that the simulated annealing parameters chosen (3000 K, 10 K, 0.95) allowed a maximum of 112 sampling phases,

each with a maximum of 10 accepted structures to be minimized, for each run less than 1120 minima were to be expected. Although it was clear, that such a low number of minima would not be sufficient to cover the conformational space of **14** ($\geq$ 15 flap atoms, 5 rotatable bonds) completely, significant differences in the efficiency of the different parameter sets could be expected. Indeed, this proved to be the case (Table III).

One common result is important: In all runs, with the exception of one (run 7), the best structures of **14** were identical (steric energy: 100.8 kcal/mol, heat of formation: -290.5 kcal/mol). This provides evidence that the global minimum of **14** has been found. Further support comes from the fact, that the x-ray structure (Fig. 9)[32a] and the calculated structure (Fig. 10) are virtually[36] the same.

Of the different flap and rotation angles used (Table III), the combination of a 60° flap and a 105° rotation performed best (run 6). In this case, the highest number of different minima and the highest number of all minima were observed, whereas no epimerizations occurred. Interestingly, perturbations by rotations of 105° (runs 4–6) gave considerably more different minima than perturbation by rotations of 120° (runs 1–3). We ascribe this to the fact that large molecules exist in a vast variety of rotamers, including those which are asymmetrically deformed.[38] Consequently, nonstaggered starting conformations, as generated by rotations of 105° or multiples thereof, must be advantageous. A second reason for the better performance of 105° rotations might be that the probability that one part of the molecule crashes into another, generating a high energy structure, is diminished. Of the flap angles used, fixed angles (90°, 60°) performed better than the Osawa flap. However,

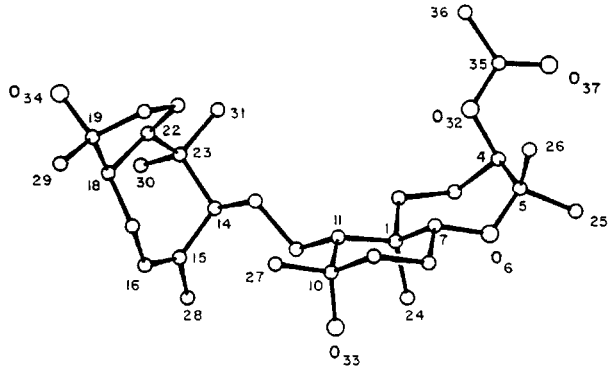


FIGURE 9. Plot of the x-ray crystal structure of **14**.

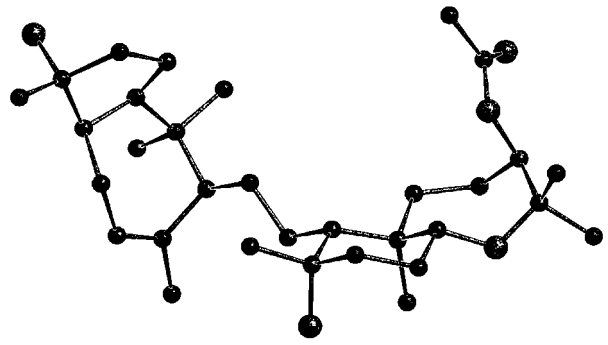


FIGURE 10. Plot of the calculated minimum structure of **14**.[37]

differing from what has been found with cycloundecane (**12**), the 60° flap performed best. Apparently, a 90° flap applied to a polycyclic system like **14** introduces so much strain that a considerable number of perturbed structures are dismissed and the minimization of the remaining structures is slow. A hint in this direction is the low final temperature of the simulated annealing in runs 2 and 5.

For the study of all other parameters, the best combination of flap and rotation angles (60°/105°) was retained. As may be seen from Table III , multiflapping and multirotation (run 7), and defining all 21 atoms as flap-atoms (run 8) resulted in a pronounced decrease in the number of minima and a concomitant production of diastereomers. In the first case, the global minimum was missed, whereas in the second case the number of different minima was the lowest of all. With both methods the efficiency of the conformational search is low. As to the process of multiflapping, this matches earlier observation by Goto and Osawa.[12b]

In two further runs we increased the number of sampling steps from 10 (run 6) to 50 (run 9) and 150 (run 10), respectively. Because after each sampling phase all perturbed structures are subjected to an energy-dependent selection criterion until the ten lowest in energy are accepted, it is easily understood that for a large number of sampling steps the acceptance rate must be high. It was therefore no surprise that, in both cases, the final temperature of the simulated annealing was high (Table III). Nevertheless, in both cases, the number of different minima and the number of all minima was lower than in run 6. Apparently, a high sampling rate is not necessarily connected with high efficiency in the conformational search. We therefore returned to the original 10 sampling steps of run 6.

TABLE III.
Calculations on Sipholenol-A Monoacetate (14). Results of the Conformational Search Using the Search Routine HUNTER with Different Parameter Sets.

Run	Number of sampling steps	Number of flaps, angle (°)	Number of rotations, angle (°)	Number of flap atoms	Final temperature (K)	Best structure[a] / hits	Number of all minima[b]	Number of different minima[b]	Number of diasteromers / number of minima[c]
1	10	1,Osawa	1,120	15	106.9	100.8/4	99	74	1/12
2	10	1,90	1,120	15	106.9	100.8/3	118	88	1/10
3	10	1,60	1,120	15	118.5	100.8/5	151	104	0/0
4	10	1,Osawa	1,105	15	145.5	100.8/1	131	101	1/17
5	10	1,90	1,105	15	112.6	100.8/2	138	109	1/6
6	10	1,60	1,105	15	178.6	100.8/4	177	125	0/0
7	50	1,60	1,105	15	330.5	100.8/1	140	103	1/2
8	150	1,60	1,105	15	255.8	100.8/1	157	118	2/6
9	10	mult.,60	mult.,105	15	82.8	103.4/2	90	81	4/9
10	10	1,60	1,105	21	153.1	100.8/3	100	68	6/11
11[d]	10	1,60	1,105	15	101.6	100.8/8	206	108	0/0
12[e]	10	1,60	1,105	15	91.7	100.8/3	211	120	0/0
13	10	1,60	1,105	15	3000.0[f]	100.8/2	170	120	1/3

[a] Steric energy (kcal / mol).
[b] Minima of stereochemically unchanged structures within 20 kcal / mol above the global minimum (100.8 kcal / mol).
[c] Different minima of all found diastereomers.
[d] Without correction of substituents.
[e] The starting structure was the structure lowest in energy, regardless whether it was new.
[f] Cooling factor: 1.0.

An interesting result emerged when the substituents were not corrected after the flapping had been performed (run 11). As compared to run 6, the number of different minima decreased, whereas the number of all minima increased. This means that, without a correction of the substituents, a higher probability of finding identical minima is connected with a lower probability of finding different minima. Therefore, correction of the substituents is indispensable.

In two final runs we investigated the influence of the initial structure (run 12) and the simulated annealing (run 13). If the initial structure for the perturbations was generally the lowest energy structure, independent of whether it was new or not, the highest number of all minima was observed. On the other hand, the more important number of different minima was slightly lower than in run 6. We therefore believe that the concept of using the structure lowest in energy which is new for the subsequent perturbation remains justified.

In the last run, the cooling factor of the simulated annealing was set to 1.0. This means that the initial temperature of 3000 K was maintained and therefore nearly all perturbed structures were accepted. Given this fact, the number of all minima and the number of different minima was surprisingly high (Table III). Apparently, the quality of the perturbed structures as generated by 60° flaps and 105° rotations is so high that the selection of low energy structure by simulated annealing becomes less important. However, for the other flap and rotation angles the situation may change.

In summary, for polycyclic systems like **14**, a perturbation by 60° flaps and 105° rotations including a correction of the substituents is most effective. Bridgehead atoms and atoms of double bonds should not be flapped and the number of sampling steps restricted to 10. The initial structure should be the structure lowest in energy which is new, and the perturbed structures subjected to a selection by simulated annealing. These parameters are combined in run 6 and gave the highest number of different minima of all. For large monocyclic systems, like **12**, and acyclic systems, like **13**, a flap angle of 90° and a rotation angle of 120°, respectively, with otherwise unchanged parameters may

be advantageous. In the following, we compare the efficiency of HUNTER with the stochastic search routine implemented in MM3(92).

CALCULATIONS WITH MM3(92)

For the efficiency of the stochastic search routine implemented in MM3(92), the choice of kick-size is crucial. Overly large kicks may result in physically unrealistic high energy structures, whereas undersize kicks may prevent that the region of the present minimum is left. Recommendations vary from 1.0 Å (cyclopentane to cyclooctane)[7b] to 3.1 Å (cycloheptadecane).[29a] Usually, a range of 1.5–3.0 Å is recommended,[12c] but for calculation with MM3(92) the recommendation is 2.0 Å.[2b] In the case of sipholenol-A monoacetate (**14**), we performed three calculations with kick-sizes of 1.5, 2.0, and 2.5 Å.

MM3(92) offers the possibility of controlling the stereochemistry of chiral centers. Therefore, the nine chiral centers of **14** (C-1,4,7,10,11,14,18,19,22) were defined in the input file. On the other hand, MM3(92) is incapable of recognizing isomerizations around double bonds. Therefore, all structures had to be checked visually as to whether the *cis*-configuration of the double bond had been preserved. MM3(92) chooses the initial structures for each perturbation cycle by an energy criterion. The corresponding parameters were set to *fran* = 1.1 and *hwith* = 0.25. To ensure an efficient reoptimization of severely contorted internal coordinates, the minimization parameter was set to *min* = 0. To make the results comparable, each simulation was allowed to run for exactly the same cpu time as HUNTER (16:00 h) on the same computer.

Two bugs in MM3(92) had to be eliminated. The first concerns the fact that, after a minimization which exceeds the time limit *tmax*, this value is set to zero, but not restored. As a consequence all following minimizations stop after the first time check. We modified MM3(92) such that *tmax* is restored after every minimization and that it now dismisses nonminimized structures, as HUNTER does. The second bug concerns the parameter *min*. This parameter controls the chirality of the perturbed structures and rejects all whose chirality has been changed. Normally, only structures with the correct chirality are minimized and, if a chirality change during minimization occurs, the corresponding structure is not stored and therefore cannot be the basis of a further peturbation. However, one exception exists: If the very first minimized structure has an altered chirality, MM3(92) uses this structure, albeit not stored, as the initial structure for the subsequent perturbations. Whenever this happens, nearly all perturbed structures will have an altered chirality and thus will be rejected. Keeping in mind, that **14** contains nine chiral centers, an endless loop of perturbations without minimization is not unlikely and in fact has been met. We therefore modified MM3(92) such that only stored structures are accepted for perturbations.

TABLE IV.
Calculations on Sipholenol-A Monoacetate (14): Results of the Conformational Search Using the Stochastic Search Routine Implemented in MM3(92) with Different Kick Parameters.

Run	Kick Size (Å)	Best structure[a] / hits	Number of all minima[b]	Number of different minima[b]
1	1.5	107.9 / 8	45	15
2	2.0	101.4 / 11	43	21
3	2.5	103.5 / 1	33	19

[a] Steric energy (kcal / mol).
[b] Minima of stereochemically unchanged structures within 20 kcal / mol above the global minimum (100.8 kcal / mol).

A last point concerns the comparison of conformers. MM3(92) compares the steric energies and the moments of inertia and defines two conformers as identical—that is, if both the difference of the steric energies and the differences in each of the three main principal axes fall below a threshold diff = $\sqrt{n_{\text{atoms}}}$. The difference of two main principal axes, I_1 and I_2, is defined as $2 \cdot (I_1 - I_2)/(I_1 + I_2)$, and for **14** (91 atoms) *diff* equals 0.095. It was clear, the for comparison purposes it had to be ensured, that the conformers recognized by HUNTER would also have been recognized by MM3(92). In most cases, the differences in the steric energies of the conformers detected by HUNTER exceeded *diff*. In all other cases the moments of inertia of the conformers in question were calculated using MM3(92), and in all cases the difference of at least one main principal axes was found to be larger than *diff*. This indicates, that the conformers detected by HUNTER would also have been detected by MM3(92).[39]

In none of the calculations with the stochastic search routine implemented in MM3(92) was the global minimum of sipholenol-A monoacetate (**13**) (steric energy: 100.8 kcal) found. Moreover, although two bugs had been eliminated, several runs had to be stopped, because endless loops of perturbations without minimization occurred. The

results of the successful runs are summarized in Table IV. The highest number of different minima was observed when the recommended kick size of 2.0 Å was used (run 2). However, even in this case, the stochastic search routine of MM3(92) was six times less effective than the new search routine HUNTER (21 vs. 125 different minima). With kick sizes of 1.5 Å (run 1) and 2.5 Å (run 3) the situation was even worse.

Summary and Conclusions

HUNTER is a new conformational search program connected to the force fields MMP2 and MM3(92). The program accepts all types of molecules (acyclic to polycyclic) with most different substructures (side chains, spirocenters, bridges), considers stereochemical facts, and covers the conformational space efficiently and completely. Its most important features are as follows: Once an input structure is created, HUNTER analyzes the connectivity, identifies π-systems, rings, chains, and rotatable bonds, locates bridgehead atoms and spirocenters and determines the stereochemistry including that of double bonds, allenes, cumulenes, and compounds with pseudoasymmetric stereogenic centers. Then the minimum set of dihedral angles to define a conformation is determined. During a subsequent stage, the latter information is used to decide whether a given conformation is new.

After the analysis of the input structure is complete, HUNTER performs the perturbation of the acyclic and cyclic parts of the molecule separately using specifically adapted perturbation methods. These comprise a modified corner flapping including a substituent correction for the cyclic parts, and an incremental rotation around single bonds for the acyclic parts. Flap atoms are user-defined, wheras rotatable bonds are recognized automatically. Double bonds may be defined as rotatable. All perturbations are effected using fixed flap and rotation angles and generally lead to physically realistic low-energy conformers of greatest diversity. To exclude physically unrealistic high energy conformers, all perturbed structures of a sampling run are subjected to a selection through simulated annealing until the ten lowest in energy are optimized. Of the structures obtained, the structure lowest in energy which is new becomes the initial structure of the next sampling run. These techniques guarantee that the conformational space is covered efficiently and completely.

HUNTER differentiates between enantiomers and diastereomers. New enantiomers are mirrored and not dismissed, and new diastereomers are stored separately. In the standard mode, a stereocheck will exclude that any stereoisomer may become the initial structure of a sampling run. However, HUNTER provides the option of a user-defined epimerization of stereogenic centers and thereby allows a convenient search for the most stable diastereomer. In all cases, a specifically devised graphic interface, SERVANT, is used to feed in and control all data necessary for a program run and to visualize the results.

The efficiency of the different parameter sets was checked in calculations with cycloundecane (**12**), (*Z*)-oct-3-ene (**13**), and sipholenol-A monoacetate (**14**). The results were as follows: For polycyclic systems, like **14**, a perturbation by 60° flaps and 105° rotations, including a correction of the substituents, performs best. Bridgehead atoms and atoms of double bonds should not be flapped. Likewise, multiflapping and multirotation should be avoided. For large monocyclic systems, like **12**, and acyclic systems, like **13**, a flap angle of 90° and a rotation angle of 120°, respectively, may be advantageous. In comparison to the widely used stochastic search routine implemented in MM3(92), HUNTER proved two (**12**) to six times (**14**) more effective. The fact that most different stereochemical facts are recognized and treated adequately is an important additional benefit. Published applications include a study on the rearrangement of (−)-β-caryophyllene (36 molecules),[17m] an investigation of the chair/twist energy gap in polyalkylcyclohexanes (93 molecules)[40] and the development of MM3 parameters for carbocations (44 molecules).[41] The program may be obtained from QCPE.[42]

Supplementary material available: Input and global minimum structures (MM3-format) and listings of the structure analyses of HUNTER for **12**, **13**, and **14** (18 pages).

Acknowledgments

We are grateful to Stephen Wilson for providing a copy of the program ANNEAL-CONFORMER and to Martina Eiffler critically reading the

manuscript. This work was supported by the Fonds der Chemischen Industrie and the Niedersachsen Fund.

References

1. N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977).
2. (a) N. L. Allinger, Y. H. Yuh, and J.-H. Lii, *J. Am. Chem. Soc.*, **111**, 8551 (1989); (b) The program and handbook [MM3(92)] may be obtained from the Quantum Chemistry program Exchange (QCPE), University of Indiana, Bloomington, IN 47405.
3. For a review, see A. E. Howard and P. A. Kollman, *J. Med. Chem.*, **31**, 1669 (1988).
4. U. Burkert and N. L. Allinger, *Molecular Mechanics*, American Chemical Society, Washington, DC, 1982.
5. (a) M. Lipton and W. C. Still, *J. Comput. Chem.*, **9**, 343 (1988); (b) Z. Li and H. A. Scheraga, *Proc. Natl. Acad. Sci. USA*, **84**, 6611 (1987); (c) G. Chang, W. C. Guida, and W. C. Still, *J. Am. Chem. Soc.*, **111**, 4379 (1989); (d) J. M. Goodman and W. C. Still, *J. Comput. Chem.*, **12**, 1110 (1991); (e) N. Weinberg and S. Wolfe, *J. Am. Chem. Soc.*, **116** 9860 (1994).
6. (a) G. M. Crippen, *Distance Geometry and Conformational Calculation*, Research Studies Press, New York, 1981; (b) P. K. Weiner, S. Profeta, Jr., G. Wipff, T. Havel, I. D. Kuntz, R. Langridge, and P. A. Kollman, *Tetrahedron*, **39**, 1113 (1983); (c) E. O. Purisima and H. A. Scheraga, *Proc. Natl. Acad. Sci. USA*, **83**, 2782 (1986); (d) G. M. Crippen and T. F. Havel, *Distance Geometry and Molecular Conformation*, Research Studies Press, New York, 1988; (e) G. M. Crippen, *J. Comput. Chem.*, **13**, 351 (1992); (f) C. E. Peishoff and J. S. Dixon, *J. Comput. Chem.*, **13**, 565 (1992); (g) C.-S. Wang, *J. Comput. Chem.*, **18**, 277 (1997).
7. (a) M. Saunders, *J. Am. Chem. Soc.*, **109**, 3150 (1987); (b) D. M. Ferguson and D. J. Raber, *J. Am. Chem. Soc.*, **111**, 4371 (1989); (c) D. M. Ferguson, W. A. Glauser, and D. J. Raber, *J. Comput. Chem.*, **10**, 903 (1989); (d) D. M. Ferguson and D. J. Raber, *J. Comput. Chem.*, **11**, 1061 (1990).
8. For example, the stochastic search routine implemented in MM3(92) failed to find several low-energy conformations including the global minimum of tricyclohexylmethane: I. Columbus and S. E. Biali, *J. Org. Chem.*, **58**, 7029 (1993).
9. H. Goto, E. Osawa, and M. Yamato, *Tetrahedron*, **49**, 387 (1993).
10. (a) I. Kolossváry and W. C. Guida, *J. Comput. Chem.*, **14**, 691 (1993); (b) I. Kolossváry and W. C. Guida, *J. Am. Chem. Soc.*, **118**, 5011 (1996).
11. H. Goto and E. Osawa, *J. Am. Chem. Soc.*, **111**, 8950 (1989).
12. (a) H. Goto and E. Osawa, *Tetrahedron Lett.*, **33**, 1343 (1992); (b) H. Goto and E. Osawa, *J. Chem. Soc. Perkin Trans.*, **2**, 187 (1993); (c) H. Goto and E. Osawa, *J. Mol. Struct.* (*Theochem*), **285**, 157 (1993).
13. For successful applications, see: (a) H. Goto, *Tetrahedron*, **48**, 7131 (1992); (b) S. D. Morley, D. E. Jackson, M. R. Saunders, and J. G. Vinter, *J. Comput. Chem.*, **13**, 693 (1992); (c) A. W. R. Payne and R. C. Glen, *J. Mol. Graph.*, **11**, 74 (1993) and Ref. 10a.
14. For some recent examples, see: (a) L. Fitjer, R. Gerke, and T. Anger, *Synthesis*, 893 (1994); (b) L. Fitjer, A. Kanschik, and M. Majewski, *Tetrahedron*, **50**, 10867 (1994); (c) L. Fitjer, B. Rissom, A. Kanschik, and E. Egert, *Tetrahedron*, **50**, 10879 (1994); (d) L. Fitjer, M. Majewski, and H. Monzó-Oltra, *Tetrahedron*, **51**, 8835 (1995).
15. J. Weiser, *CAtionic REarrangements in SYnthesis*, Ph.D. thesis, University of Göttingen, Göttingen, Germany, 1996.
16. (a) P. v. R. Schleyer, L. K. M. Lam, D. J. Raber, J. L. Fry, M. A. McKervey, J. R. Alford, B. D. Cuddy, V. G. Keizer, H. W. Geluk, and J. L. M. A. Schlatmann, *J. Am. Chem. Soc.*, **92**, 5246 (1970); (b) D. M. Brouwer and H. Hogeveen, *Recl. Trav. Chim. Pays-Bas*, **89**, 211 (1970); (c) A. Nickon and R. C. Weglein, *J. Am. Chem. Soc.*, **97**, 1271 (1975); (d) M. Saunders, J. Chandrasekhar, and P. v. R. Schleyer, In *Rearrangements in Ground and Excited States, Vol. 1*, P. de Mayo, Ed., Academic Press, New York, 1980, pp. 1–53.
17. For an excellent review, see: (a) K. B. Lipkowitz and M. A. Peterson, *Chem. Rev.*, **93**, 2463 (1993). Selected applications: search for the most stable diastereomer: (b) M. Saunders, *Science*, **253**, 330 (1991); (c) P. Tarakeshwar, J. Iqbal, and S. Manogaran, *Tetrahedron*, **47**, 297 (1991). Modeling of diastereomeric transition states: (d) L. F. Tietze, H. Geissler, J. Fennen, T. Brumby, S. Brand, and G. Schulz, *J. Org. Chem.*, **59**, 182 (1994); (e) K. Takatori, M. Kajiwara, Y. Sakamoto, T. Shimayama, H. Yamada, and T. Takahashi, *Tetrahedron Lett.*, **35**, 5669 (1994). Modeling of inversion processes: (f) A. Peyman and H.-D. Beckhaus, *J. Comp. Chem.*, **13**, 541 (1992); (g) I. Kolossváry and W. C. Guida, *J. Mol. Struct.* (*Theochem*), **308**, 91 (1994); (h) J. H. Brown and C. H. Bushweller, *J. Phys. Chem.*, **98**, 11411 (1994). Modeling of conformationally controlled reactions: (i) J. M. Goodman, S. D. Kahn, and I. Paterson, *J. Org. Chem.*, **55**, 3295 (1990); (j) T. Takahashi, H. Yokoyama, H. Yamada, T. Haino, and Y. Fukazawa, *Synlett*, **7**, 494 (1993); (k) M. P. Polovinka, D. V. Korchagina, Y. V. Gatilov, I. Y. Bagrianskaya, V. A. Barkhash, V. V. Shcherbukhin, N. S. Zefirov, V. B. Perutskii, N. D. Ungur, and P. F. Vlad, *J. Org. Chem.*, **59**, 1509 (1994); (l) H. Suginome, T. Kondoh, C. Gogonea, V. Singh, H. Goto, and E. Osawa, *J. Chem. Soc. Perkin Trans*, **1**, 69 (1995); (m) L. Fitjer, A. Malich, C. Paschke, S. Kluge, R. Gerke, B. Rissom, J. Weiser, and M. Noltemeyer, *J. Am. Chem. Soc.*, **117**, 9180 (1995).
18. M. Saunders, *J. Comput. Chem.*, **10**, 203 (1989), and Ref. 2.
19. J. T. Sprague, J. C. Tai, Y. Yuh, and N. L. Allinger, *J. Comput. Chem.*, **8**, 581 (1987).
20. *PC-Model, Version 4.0*, Serena Software, P.O. Box 3076, Bloomington, IN 47402.
21. S. Kirkpatrick, C. D. Gelatt, Jr., and M. P. Vecchi, *Science*, **220**, 671 (1983).
22. (a) M. Plotkin, *J. Chem. Doc.*, **11**, 60 (1971); (b) J. Gasteiger and C. Jochum, *J. Chem. Inf. Comput. Sci.*, **19**, 43 (1979). For a review, see: (c) G. M. Downs, V. J. Gillet, J. D. Holliday, and M. F. Lynch, *J. Chem. Inf. Comput. Sci.*, **29**, 172 (1989).
23. M. Frèrejacque, *Bull. Soc. Chim. Fr.*, **6**, 1008 (1939).
24. L. Baumer, G. Sala, and G. Sello, *Computers Chem.*, **15**, 293 (1991).
25. (a) R. S. Cahn and C. K. Ingold, *J. Chem. Soc.*, 612 (1951); (b) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); (c) R. S. Cahn, *J. Chem. Ed.*, **41**, 116 (1964); (d) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem.*, **78**, 413 (1966); *Angew. Chem. Int. Ed. Engl.*, **5**, 385 (1966); (e) V. Prelog and G. Helmchen, *Angew. Chem.*, **94**, 614 (1982); *Angew. Chem., Int. Ed. Engl.*, **21**, 567 (1982).

26. P. Mata, A. M. Lobo, C. Marshall, and A. P. Johnson, *J. Chem. Inf. Comput. Sci.*, **34**, 491 (1994).
27. (a) R. H. Custer, *Match*, **21**, 3 (1986); (b) H. Dodziuk and M. Mirowicz, *Tetrahedron: Asymmetry*, **1**, 171 (1990); (c) P. Mata, A. M. Lobo, C. Marshall, and A. P. Johnson, *Tetrahedon: Asymmetry*, **4**, 657 (1993).
28. M. Razinger and M. Perdih, *J. Chem. Inf. Comput. Sci.*, **34**, 290 (1994), and references therein; (b) K. K. Agarwal and H. L. Gelernter, *J. Chem. Inf. Comput. Sci*, **34**, 463 (1994), and references therein.
29. (a) M. Saunders, K. N. Houk, Y.-D. Wu, W. C. Still, M. Lipton, G. Chang, and W. C. Guida, *J. Am. Chem. Soc.*, **112**, 1419 (1990); (b) M. Saunders, *J. Comput. Chem.*, **12**, 645 (1991); (c) I. Kolossváry and W. C. Guida, *J. Chem. Inf. Comput. Sci.*, **32**, 191 (1992), and Refs. 7b, 12a, and 13a.
30. N. Metropolis, A. W. Rosenbluth, M. N. Rosenbluth, A. H. Teller, and E. Teller, *J. Chem. Phys.*, **21**, 1087 (1953).
31. For applications, see: (a) R. A. Donnelly, *Chem. Phys. Lett.*, **136**, 274 (1987); (b) S. R. Wilson, W. Cui, J. W. Moskowitz, and K. E. Schmidt, *Tetrahedron Lett.*, **29**, 4373 (1988); (c) J. W. Moskowitz, K. E. Schmidt, S. R. Wilson, and W. Cui, *Int. J. Quant. Chem. Quant. Chem. Symp.*, **22**, 611 (1988); (d) R. H. J. M. Otten and L. P. P. P. van Ginneken, *The Annealing Algorithm*, Kluwer, Boston, 1989; (e) M. T. Barakat and P. M. Dean, *J. Comput.-Aided Molec. Design*, **4**, 295 (1990); (f) I. M. Navon, F. B. Brown, and D. H. Robertson, *Computers Chem.*, **14**, 305 (1990); (g) S. R. Wilson, W. Cui, J. W. Moskowitz, and K. E. Schmidt, *J. Comput. Chem.*, **12**, 342 (1991); (h) S. H. Nilar, *J. Comput. Chem.*, **12**, 1008 (1991); (i) F. Guarnieri and S. R. Wilson, *Tetrahedron*, **48**, 4271 (1992); (j) M. E. Snow, *J. Comput. Chem.*, **13**, 579 (1992), and Ref. 13b.
32. (a) U. Shmueli, S. Carmely, A. Groweiss, and Y. Kashman, *Tetrahedron Lett.*, **22**, 709 (1981). Systematic name: decahydro-2,2,5a,7-tetramethyl-6-[2-(1,2,3,3a,4,5,8,8a-octahydro-1-hydroxy-1,4,4,6-tetramethyl-5-azulenyl)-ethyl] - 1-benzoxepin-3,7-diol-3-acetate. We have taken the trivial name from: (b) S. Carmely and Y. Kashman, *J. Org. Chem.*, **48**, 3517 (1983).
33. I. Kolossváry and W. C. Guida, *J. Am. Chem. Soc.*, **115**, 2107 (1993), and Ref. 5e, 12b, and 29b.
34. The maximum optimization time for each run of the local optimizers followed from a series of preliminary calculations and was chosen so as to avoid wasting CPU time due to unsuccessful optimizations.
35. The calculations were performed at the Gesellschaft für wissenschaftliche Datenverarbeitung mbH, Göttingen (GWDG).
36. We originally located sipholenol-A monoacetate (**13**) as interesting test case for a conformational search in *Molecular Structures and Dimensions*, University Press, Cambridge, *Vol. 13*, 1982, p. 109 and D97. After the calculations had been completed, we became aware of the fact that no crystal structure data had been deposited and that the data no longer exist (personal communication from U. Shmueli, University of Tel-Aviv). We apologize for this fact.
37. The ball-and-stick model was made with the assistance of SCHAKAL: E. Keller, *Chem. Unserer Zeit*, **6**, 178 (1986).
38. (a) K. B. Wiberg and M. A. Murcko, *J. Am. Chem. Soc.*, **110**, 8029 (1988); (b) S. Tsuzuki, L. Schäfer, H. Goto, E. D. Jemmis, H. Hosoya, K. Siam, K. Tanabe, and E. Osawa, *J. Am. Chem. Soc.*, **113**, 4665 (1991), and Ref. 9.
39. On the contrary, spot checks revealed several cases where two conformations were defined different by MM3(92), but identical by HUNTER. In these cases the energy difference exceeded *diff*, whereas the dihedral angles did not differ by more than 2°.
40. J. Weiser, O. Golan, L. Fitjer, and S. E. Biali, *J. Org. Chem.*, **61**, 8277 (1996).
41. D. Strobl, J. Weiser, and L. Fitjer, *Tetrahedron*, **53**, 2767 (1997).
42. HUNTER for MM3 (Unix) and SERVANT (Dos), QCPE #674, Quantum Chemistry Program Exchange (QCPE), University of Indiana, Bloomington, IN 47405.